

CLINICAL INVESTIGATION PLAN FOR THE ZENITH® LOW PROFILE AAA ENDOVASCULAR GRAFT

Zenith® Low Profile AAA Endovascular Graft Clinical Study

Version: 08-013-06
Version Date: 06 November 2013

Sponsor and Manufacturer:

Cook Incorporated

750 Daniels Way

Bloomington, IN 47404

USA

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

This clinical trial will be conducted in compliance with the clinical investigation plan, ISO 14155, ICH GCP, 21 CFR 812, and other applicable requirements as appropriate.

Sponsor Contact

Signature

DD/Mon/YYYY

Printed Name

Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T.

Coordinating Clinical Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature

DD/Mon/YYYY

Printed Name

Title

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE, CON'T

Principal Clinical Investigator

I hereby confirm that I approve of this Clinical Investigation Plan and agree to comply with its terms as laid out in this document.

Signature

DD/Mon/YYYY

Printed Name

Title

CONFIDENTIALITY STATEMENT

This document shall be treated as a confidential document for the sole information and use of the clinical investigation team and the Ethics Committee/IRB.

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Attachments

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1.0 General Information

1.1 Sponsor and Manufacturer

Cook Incorporated

750 Daniels Way

Bloomington, IN 47404

Contact: [REDACTED]

Telephone: [REDACTED]

Fax: [REDACTED]

E-mail: [REDACTED]

1.2 Data Coordinating Center/Monitor

MED Institute, Inc.

1 Geddes Way

West Lafayette, IN 47906

Contact: [REDACTED]

Telephone: [REDACTED]

Fax: [REDACTED]

E-mail: [REDACTED]

1.3 Study Administration

This study will be conducted in compliance with global regulations (e.g., ICH GCP, ISO 14155, 21 CFR 812, and other regulations as applicable).

1.4 Investigators

Contact information for the Global Principal Investigator and principal investigators will be provided in the investigator file. The contact information and qualifications for the Global Principal Investigator, principal investigators and coordinating investigators, and core laboratory will be updated and maintained by the Data Coordinating Center.

1.5 Insurance

The devices are covered by the sponsor's product liability insurance. A clinical study insurance policy will be taken out according to local requirements.

1.6 Monitoring Arrangements

The conduct of the clinical study will be supervised through a process of centralized and on-site monitoring. The data coordinating center will remotely monitor the study for data completeness and for adverse events. On-site monitoring will be implemented as necessary throughout the course of the study. The investigator/institution will provide direct access to source data/documents for study-related monitoring, audits, Ethics Committee/IRB review and regulatory inspection. Written procedures for monitoring the investigation are maintained by the monitor and are provided in Attachment 1.

Name and Address of the Monitor:

MED Institute, Inc. or designee
1 Geddes Way
West Lafayette, IN 47906

Contact:

Telephone:

Fax:

E-mail:



1.7 Data Management and Quality Assurance

The principal investigator or appropriately trained designee at each investigative site will complete standardized, data collection forms in an electronic data capturing (EDC) system (see section 16). The completed data forms and other patient documents pertaining to the study will be reviewed, processed, and stored by the sponsor. Data will be reviewed for missing data, data consistency, and reasonableness of responses. Discrepancies will be resolved through a formal query process involving direct contact with investigators or research coordinators. The data coordinating center is responsible for database management, data verification, data archiving, and data retention

Pertinent imaging (pre-procedure, procedural, and follow-up) will be sent to MED Institute, who will coordinate shipment of imaging for independent analysis.

As needed to assist the sponsor in its research (e.g., during evaluation of an adverse event), data will be accessible to the sponsor, the participating investigators, the manufacturer, and companies or individuals the sponsor authorizes.

MED Institute, Inc., the data coordinating center, maintains a Safe Harbor Privacy Policy that describes the privacy principles followed with respect to the transfer of personal information from member states in Europe to the United States.

2.0 Approvals and Agreements

The sponsor, Global Principal Investigator, and the principal clinical investigators for each site shall agree to this document and any modifications. A justification for any modifications will be documented. Approval and agreement will be indicated by signing and dating the appropriate document.

3.0 Clinical Investigation Plan Overview

This clinical investigation is designed as a prospective non-randomized study enrolling up to 120 patients to receive the Zenith® Low Profile AAA Endovascular Graft main body in conjunction with the Zenith® Spiral-Z® AAA Iliac Leg Graft at up to 40 global clinical sites with a maximum enrollment of up to 24 patients per individual site. The objective of the study is to evaluate the safety and effectiveness of the Zenith Low Profile AAA Endovascular Graft used in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft. Freedom from major adverse events (MAEs) at 30 days and device success at 12 months for this treatment cohort will be compared to their respective performance goals derived from the results of the Zenith® AAA Endovascular Graft clinical study.

Any patient with an abdominal aortic, aortoiliac, or iliac aneurysm and suitable for treatment with the Zenith Low Profile AAA Endovascular Graft with the 16 Fr or 17 Fr H&L-B One-Shot™ Introduction System in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft with the Z-Trak® Introduction System is eligible for enrollment in the study. The study flow diagram is presented in Figure 1.

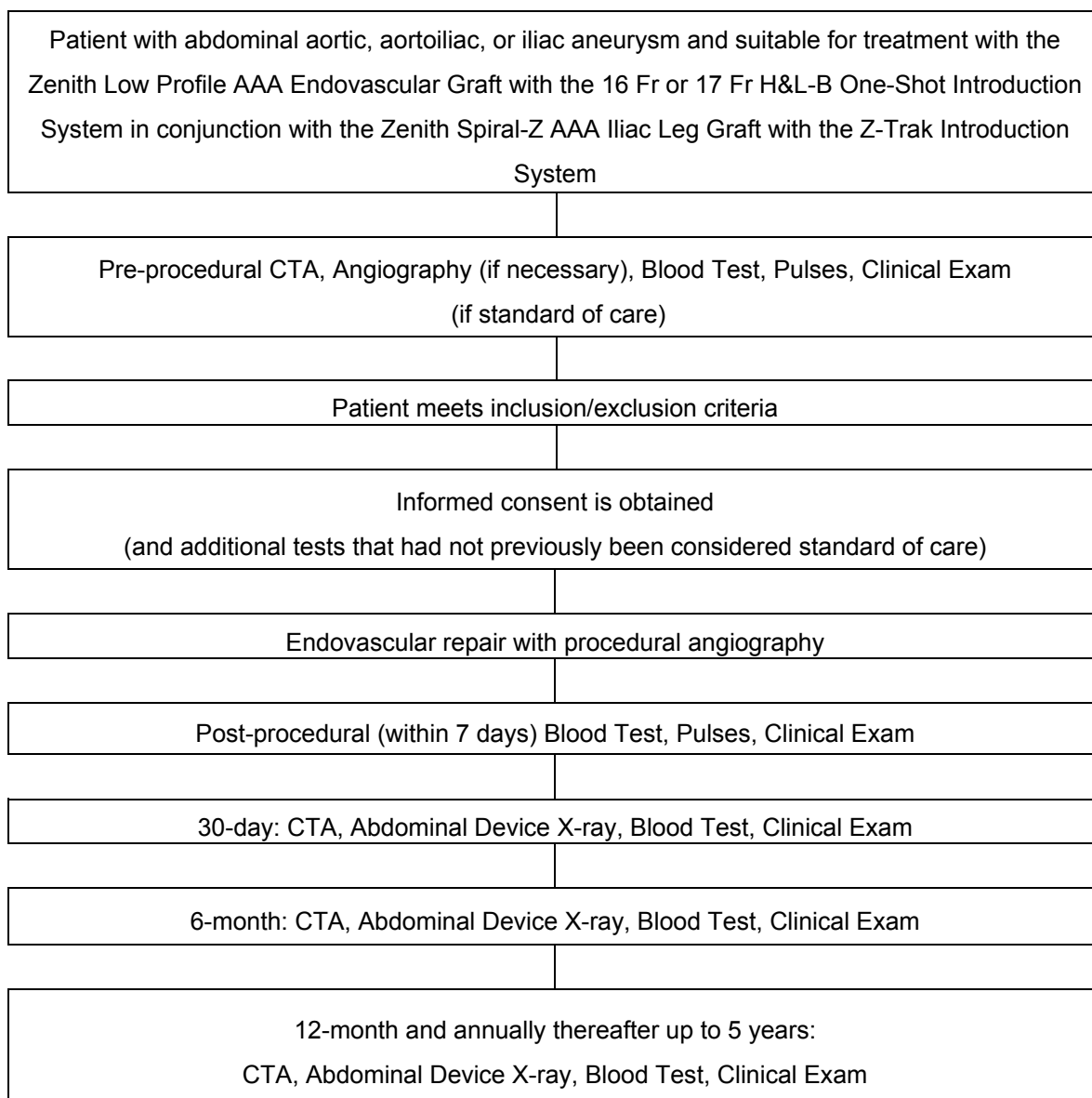


Figure 1. Study flow diagram

4.0 Objectives of the Clinical Investigation

4.1 Objective

The objective of the study is to evaluate the safety and effectiveness of the Zenith Low Profile AAA Endovascular Graft used in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft. The safety endpoint will be freedom from MAEs at 30 days and the effectiveness endpoint will be device success at 12 months.

4.2 Claims and Intended Performance that are to be Verified

The following data points will be evaluated to verify device performance:

- Device success (including technical success)
- Procedural times
- Access method (percutaneous, cutdown, or conduit usage) employed during the procedure
- Clinical utility measures
- Morbidity, including Major Adverse Events (MAEs) as well as events distal to the graft limb (e.g., arterial thrombosis)
- Reinterventions-
- Endoleak, change in aneurysm size, migration, device patency, device integrity

4.3 Specific Hypotheses to be Accepted or Rejected by Statistical Data

The safety endpoint of 30-day freedom from MAEs will be analyzed on a per patient basis. The analysis requires that the agreed upon performance goal of 88%, which was derived from the 30-day freedom from MAE rate for patients treated with the currently approved Zenith AAA Endovascular Graft, be met. The performance goal will be said to have been met provided that the null hypothesis is rejected in favor of the alternate with a one-tailed exact binomial test at the 0.025-level. Given that $\pi_{\text{MAE}(30)}$ is the probability that a randomly selected patient experienced freedom from MAEs at 30 days, the null and alternate hypotheses are as follows.

Null Hypothesis: The 30-day freedom from MAEs for patients treated with the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft does not meet the performance goal (88%).

$$H_0: \pi_{\text{MAE}(30)} < 88\%$$

Alternate Hypothesis: The 30-day freedom from MAEs for patients treated with the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft meets the performance goal (88%).

$$H_A: \pi_{\text{MAE}(30)} \geq 88\%$$

[REDACTED]

Similarly, the effectiveness endpoint of 12-month device success will be analyzed on a per patient basis. The analysis requires that the agreed upon performance goal of 83%, which was derived from the 12-month device success rate for patients treated with the currently approved Zenith AAA Endovascular Graft, be met. The performance goal will be said to have been met provided that the null hypothesis is rejected in favor of the alternate with a one-tailed exact binomial test at the 0.025-level. Given that $\pi_{DS(12)}$ is the probability that a randomly selected patient experienced device success at 12 months, the null and alternate hypotheses are as follows.

Null Hypothesis: The 12-month device success for patients treated with the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft does not meet the performance goal (83%).

$$H_0: \pi_{DS(12)} < 83\%$$

Alternate Hypothesis: The 12-month device success for patients treated with the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft meets the performance goal (83%).

$$H_A: \pi_{DS(12)} \geq 83\%$$

[REDACTED]

5.0 Device Description and Intended Purpose

5.1 Device Identification

The name of the device is the Zenith Low Profile AAA Endovascular Graft which is used in conjunction with the commercially available Zenith Spiral-Z AAA Iliac Leg Graft.

The following main body (Table 5.1-1), iliac leg (Table 5.1-2), and ancillary device sizes (Tables 5.1-3 and 5.1-4) will be available for the study:

Table 5.1-1. Zenith Low Profile AAA Endovascular Graft Main Body Graft Size Availability*

ZALB-22-70	ZALB-24-70	ZALB-26-70	ZALB-28-70	ZALB-30-70	ZALB-32-70	ZALB-36-70
ZALB-22-84	ZALB-24-84	ZALB-26-84	ZALB-28-84	ZALB-30-84	ZALB-32-84	ZALB-36-84
ZALB-22-98	ZALB-24-98	ZALB-26-98	ZALB-28-98	ZALB-30-98	ZALB-32-98	ZALB-36-98
ZALB-22-108	ZALB-24-108	ZALB-26-108	ZALB-28-108	ZALB-30-108	ZALB-32-108	ZALB-36-108
ZALB-22-118	ZALB-24-118	ZALB-26-118	ZALB-28-118	ZALB-30-118	ZALB-32-118	ZALB-36-118
ZALB-22-128	ZALB-24-128	ZALB-26-128	ZALB-28-128	ZALB-30-128	ZALB-32-128	ZALB-36-128

* Graft sizes are ZALB-XX-YY where XX mm is the proximal graft diameter and YY mm is the length from the proximal graft edge to the distal end of the contralateral leg.

Table 5.1-2. Zenith Spiral-Z AAA Iliac Leg Graft Size Availability*

ZSLE-9-39	ZSLE-11-39	ZSLE-13-39	ZSLE-16-39	ZSLE-20-39	ZSLE-24-39
ZSLE-9-56	ZSLE-11-56	ZSLE-13-56	ZSLE-16-56	ZSLE-20-56	ZSLE-24-56
ZSLE-9-74	ZSLE-11-74	ZSLE-13-74	ZSLE-16-74	ZSLE-20-74	ZSLE-24-74
ZSLE-9-90	ZSLE-11-90	ZSLE-13-90	ZSLE-16-90	ZSLE-20-90	ZSLE-24-90
ZSLE-9-107	ZSLE-11-107	ZSLE-13-107			
ZSLE-9-122	ZSLE-11-122	ZSLE-13-122			

* Graft sizes are ZSLE-XX-YY where XX mm is the distal graft diameter and YY mm is the working length (from the distal edge of the overlap zone to the distal edge of the graft material).

Table 5.1-3. Zenith Low Profile AAA Endovascular Graft Main Body Extension Graft Size Availability*

ZLBE-22-45	ZLBE-24-45	ZLBE-26-45	ZLBE-28-45	ZLBE-30-45	ZLBE-32-45	ZLBE-36-45
ZLBE-22-58	ZLBE-24-58	ZLBE-26-58	ZLBE-28-58	ZLBE-30-58	ZLBE-32-58	ZLBE-36-58

* Graft sizes are ZLBE-XX-YY where XX mm is the proximal graft diameter and YY mm is the graft length.

Table 5.1-4. Zenith Low Profile AAA Endovascular Graft Converter Graft Size Availability*

ZLC-24-66	ZLC-28-66	ZLC-32-66	ZLC-36-66
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* Graft sizes are ZLC-XX-YY where XX mm is the proximal graft diameter and YY mm is the graft length.

Devices under investigation will be tracked by the clinical site throughout the course of the clinical study. This includes information such as lot numbers, quantity, and disposition of devices. Additionally, information such as the quantity, size(s), and lot number(s) of devices used in patients will be recorded on Case Report Forms (CRFs).

5.2 Intended Purpose

The Zenith Low Profile AAA Endovascular Graft with the Zenith Spiral-Z AAA Iliac Leg Graft and ancillary components are indicated for the endovascular treatment of patients with abdominal aortic, aorto-iliac, or iliac aneurysms having morphology suitable for endovascular repair, including:

- Iliac/femoral anatomy that is suitable for access with a 16 Fr (6.0 mm nominal sheath O.D.) or 17 Fr (6.5 mm nominal sheath O.D.) introduction system;
- Non-aneurysmal infrarenal aortic segment (neck) proximal to the aneurysm:
 - with a length of at least 15 mm,
 - with a diameter measured outer wall to outer wall of no greater than 32 mm and no less than 18 mm,
 - with an angle less than 60 degrees relative to the long axis of the aneurysm, and
 - with an angle less than 45 degrees relative to the axis of the suprarenal aorta; and
- Iliac artery distal fixation site greater than 10 mm in length and 7.5-20 mm in diameter (measured outer wall to outer wall).

5.3 General Device Description

A general device description, including any materials that will be in contact with tissues or body fluids can be located in the Clinical Investigator Brochure. The device does not contain medicinal products, human and/or animal tissues or their derivatives, or other biologically active substances.

5.4 Photographs of Device

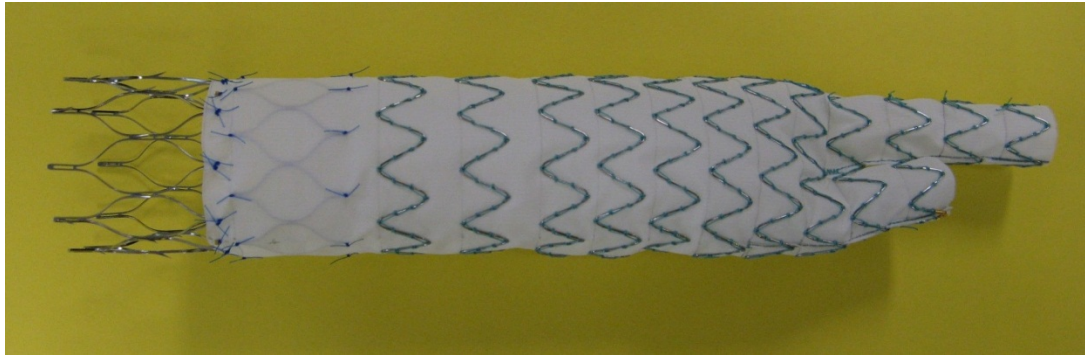


Figure 2. Zenith Low Profile AAA Endovascular Graft Main Body

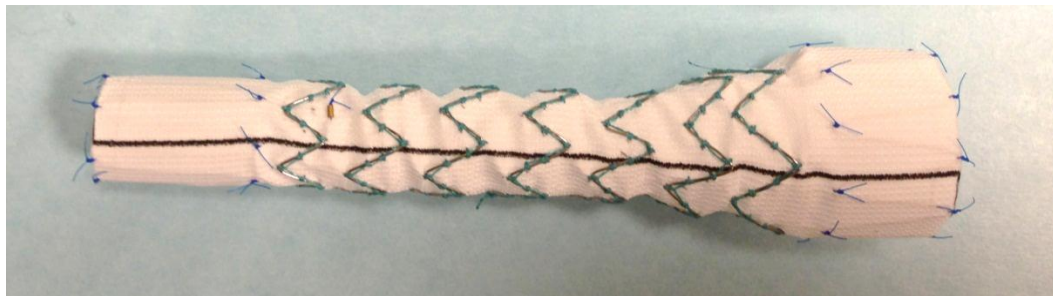


Figure 3. Zenith Spiral-Z AAA Iliac Leg Graft



Figure 4. Zenith Low Profile AAA Endovascular Graft Introduction System

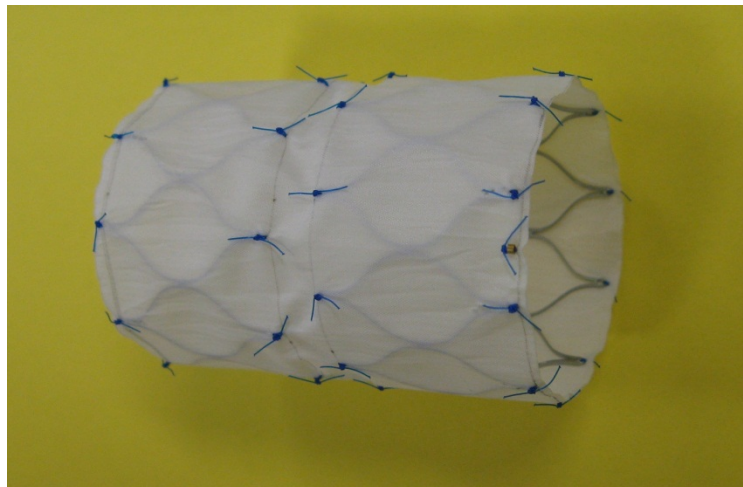


Figure 5. Zenith Low Profile AAA Endovascular Graft Main Body Extension

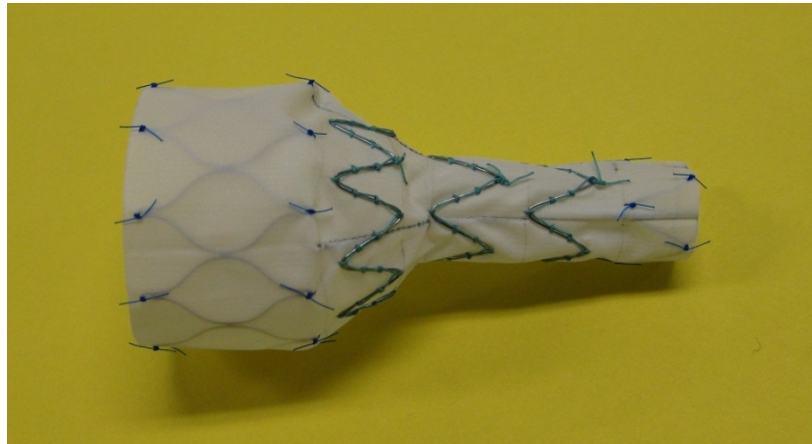


Figure 6. Zenith Low Profile AAA Endovascular Graft Converter

The Zenith Iliac Plug, which is commercially available, may be used in conjunction with the Zenith Low Profile AAA Endovascular Graft Converter to convert the patient to an aortouni-iliac configuration, if necessary.

5.5 Instructions for Use and Implantation

Please reference the manufacturer's Instructions for Use for complete instructions including implantation, storage and handling requirements, preparation for use, pre-use checks for safety and performance, and precautions to be taken after use.

5.6 Summary of Necessary Training and Experience

The Zenith Low Profile AAA Endovascular Graft and Zenith Spiral-Z AAA Iliac Leg Graft should be deployed by investigators trained and experienced in endovascular procedures. Please refer to the manufacturer's Instructions for Use for a complete summary of the necessary training and experience required for use of these devices.

5.7 Description of the Necessary Medical or Surgical Procedures

Please refer to the manufacturer's Instructions for Use for a complete description of the procedures involved in the use of these devices.

6.0 Preliminary Investigations and Justification

6.1 Literature Review

Please refer to the Clinical Investigator Brochure for a complete literature review and evaluation.

6.2 Non-clinical Testing

Non-clinical tests were conducted in accordance with Good Laboratory Practice requirements, or performed in compliance with verified methods and Standard Operating Procedures to maintain the integrity of the results. *In vitro* testing has established reasonable safety of the device for the duration of the study and in the trial population to be studied. Please refer to the Clinical Investigator Brochure for a summary of non-clinical testing.

6.3 Previous Clinical Experience

Please refer to the Clinical Investigator Brochure for a complete description of the previous clinical experiences with these devices and other similar devices.

7.0 Risk Analysis and Risk Assessment

Please refer to the Clinical Investigator Brochure for a complete risk analysis.

7.1 Risks and Foreseeable Adverse Device Effects

Risks of adverse events are likely to be similar to those reported in recent studies of other endovascular AAA grafts. Adverse events associated either with the Zenith Low Profile AAA Endovascular Graft, the Zenith Spiral-Z AAA Iliac Leg Graft, or the implantation procedure that may occur and require intervention include, but are not limited to:

- Amputation
- Anesthetic complications and subsequent attendant problems (e.g., aspiration)
- Aneurysm enlargement
- Aneurysm rupture and death
- Aortic damage, including perforation, dissection, bleeding, rupture and death
- Arterial or venous thrombosis and/or pseudoaneurysm
- Arteriovenous fistula
- Bleeding, hematoma, or coagulopathy
- Bowel complications (e.g., ileus, transient ischemia, infarction, necrosis)
- Cardiac complications and subsequent attendant problems (e.g., arrhythmia, myocardial infarction, congestive heart failure, hypotension, hypertension)
- Claudication (e.g., buttock, lower limb)
- Death
- Edema

- Embolization (micro and macro) with transient or permanent ischemia or infarction
- Endoleak
- Endoprosthesis: improper component placement; incomplete component deployment; component migration; suture break; occlusion; infection; stent fracture; graft material wear; dilatation; erosion; puncture; perigraft flow; barb separation and corrosion
- Fever and localized inflammation
- Genitourinary complications and subsequent attendant problems (e.g., ischemia, erosion, fistula, incontinence, hematuria, infection)
- Graft or native vessel occlusion
- Hepatic failure
- Impotence
- Infection of the aneurysm, device or access site, including abscess formation, transient fever and pain
- Lymphatic complications and subsequent attendant problems (e.g., lymph fistula)
- Neurologic local or systemic complications and subsequent attendant problems (e.g., stroke, transient ischemic attack, paraparesis, paralysis)
- Pulmonary/respiratory complications and subsequent attendant problems (e.g., pneumonia, respiratory failure, prolonged intubation)
- Renal complications and subsequent attendant problems (e.g., artery occlusion, contrast toxicity, insufficiency, failure)
- Surgical conversion to open repair
- Vascular access site complications, including infection, pain, hematoma, pseudoaneurysm, or arteriovenous fistula
- Vascular spasm or vascular trauma (e.g., iliofemoral vessel dissection, bleeding, rupture, death)
- Vessel damage
- Wound complications and subsequent attendant problems (e.g., dehiscence, infection)

7.2 Methods to Minimize Risks

The device design, non-clinical testing, clinical study design, and the Instructions for Use are intended to minimize the risks associated with the endovascular procedures.

8.0 Design of the Clinical Investigation

8.1 Type of Investigation

The current investigation is a prospective, non-randomized, non-blinded study.

8.2 Rationale

The assessment of safety will be based on freedom from MAEs at 30 days and the assessment of effectiveness will be based on device success at 12 months.

8.3 Measures to be Taken to Avoid or Minimize Bias

This study is not randomized or blinded, as it is intended to prospectively collect information regarding the safety and effectiveness of the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft. Similar inclusion/exclusion criteria will be used during patient selection for the current patient cohort compared to that for the Zenith AAA Endovascular Graft clinical study, which was the basis for the chosen performance goals.

8.4 Variables to be Measured to Demonstrate Achievement of Endpoints

To evaluate deployment characteristics and procedural outcome, the following data points will be collected intra-operatively:

- 1) Assessment of system performance including: deployment issues, ease of insertion, visualization, and ease of removal
- 2) Complications (if any)
- 3) Ancillary equipment needed
- 4) Adjunctive maneuvers including: balloon dilation of iliac arteries, additional stents required, and additional surgical procedures
- 5) Findings of completion assessment: minimum iliac leg graft lumen diameter, device patency, endoleak, and kinks

In addition, the results of the endovascular repair will be assessed by clinical and/or imaging evaluation at the time of graft insertion, within 7 days post-procedure, at 30 days [REDACTED], 6 months [REDACTED], 12 months [REDACTED], 2 years [REDACTED], 3 years [REDACTED], 4 years [REDACTED], and 5 years [REDACTED] according to the post-operative study schedule below. [REDACTED]
[REDACTED]

Study Schedule						
	Pre-op	Intra-op	Post-procedure	30-Day	6-Month	12-Month ⁵
Clinical Exam	X		X	X	X	X
Pulses	X		X			
Blood Test ¹	X		X	X	X	X
CTA	X ²			X ⁴	X ⁴	X ⁴
Abdominal Device X-ray				X	X	X
Angiography	X ³	X				
¹ Blood test for serum creatinine. ² Imaging should be performed within 6 months prior to implant procedure. ³ Required only to resolve any uncertainties in anatomical measurements necessary for graft sizing. ⁴ A non-contrast CT in conjunction with a duplex ultrasound may be used for those patients experiencing renal failure or who are otherwise unable to undergo contrast enhanced CT scan. ⁵ Yearly thereafter through 5 years.						

8.5 Inclusion/Exclusion Criteria

Patients must meet at least one of the inclusion criteria below to be enrolled in the study. General and medical exclusion criteria will be assessed during the initial patient evaluation by conducting a history and physical examination. Anatomical exclusion criteria will be assessed using a variety of imaging techniques that are routinely performed during the evaluation of abdominal aortic aneurysms. Sectional imaging will be performed by CT scan.

Angiography and intravascular ultrasound will be performed as needed to further assess inclusion/exclusion criteria.

Assessment of entry criteria will be based upon data available pre-operatively. Data obtained peri-operatively and post-operatively (including the results from core lab analysis of pre-procedure imaging) may contradict pre-operative assessment. However, such contradiction is not considered a protocol violation and should not be construed as evidence of inadequate or inaccurate pre-operative assessment with respect to the enrollment criteria or evidence of inappropriate enrollment. Enrollment is to be based upon best available pre-operative data. Therefore, some criteria relate to subjective assessment while other criteria are considered absolute and able to be determined definitively. Variability in assessment between centers, investigators and observers is expected with several criteria.

8.5.1 Inclusion Criteria

A patient is deemed suitable for inclusion in the study if the patient has at least one of the following AND is suitable for treatment with the Zenith Low Profile AAA Endovascular Graft with the 16 Fr (for 22 – 32 mm diameter grafts) or 17 Fr (for 36 mm diameter graft) H&L-B One-Shot Introduction System in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft with the Z-Trak Introduction System:

- 1) Aortic or aortoiliac aneurysm with a diameter ≥ 5.0 cm for males or ≥ 4.5 cm for females
- 2) Iliac aneurysm with a diameter ≥ 3.0 cm
- 3) Aneurysm with a history of growth ≥ 0.5 cm per year.

8.5.2 Exclusion Criteria

Patients must be excluded from the study if any of the following conditions are true:

General Exclusion Criteria

- 1) Less than 18 years of age
- 2) Other current conditions (e.g., cancer, systemic infection) that may cause the patient to be noncompliant with the clinical investigation plan, that may confound the results, or that is associated with a life expectancy less than 2 years
- 3) Pregnant or breastfeeding or planning on becoming pregnant within 60 months
- 4) Unwilling to comply with the follow-up schedule
- 5) Inability or refusal to give informed consent
- 6) Less than 30 days beyond primary endpoint for other investigative drug or device study

Medical Exclusion Criteria

- 1) Known sensitivities or allergies to nitinol (nickel, titanium), polyester, polypropylene, gold, stainless steel, or solder (tin, silver)
- 2) History of anaphylactic reaction to contrast material that cannot be adequately premedicated
- 3) Leaking/ruptured or symptomatic aneurysm
- 4) Uncorrectable coagulopathy
- 5) Planned interventional or surgical procedure that is unrelated to AAA repair within 30 days before or after AAA repair

Anatomical Exclusion Criteria

- 1) Significant occlusive disease, tortuosity, or calcification
- 2) Proximal neck <15 mm in length
- 3) Proximal neck, measured outer wall to outer wall on a sectional image (CT) > 32 mm in diameter or <18 mm in diameter
- 4) Proximal neck angulated more than 60 degrees relative to the long axis of the aneurysm
- 5) Immediate suprarenal neck angulated more than 45 degrees relative to the immediate infrarenal neck
- 6) Proximal seal site with inverted funnel shape (change in neck diameter > 10% over the first 15 mm of proximal neck length)
- 7) Proximal seal site with circumferential thrombus/atheroma
- 8) Aortic diameter, measured inner wall to inner wall on a sectional image (CT), < 20 mm just proximal to the aortoiliac bifurcation
- 9) Iliac/femoral anatomy that is unsuitable for access with the 16 Fr (6.0 mm nominal sheath O.D.) or 17 Fr (6.5 mm nominal sheath O.D.) introduction system
- 10) Iliac artery diameter, measured outer wall to outer wall on a sectional image (CT), > 20 mm or < 7.5 mm at distal fixation site
- 11) Iliac artery distal fixation site < 10 mm in length
- 12) Indispensable inferior mesenteric artery (IMA)
- 13) Inability to maintain at least one patent hypogastric artery
- 14) Renal artery stenosis > 80% (and serum creatinine > 2.0 mg/dl)
- 15) Unsuitable arterial anatomy

8.6 Patient Consent

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be invited to participate in this study. All patients eligible for entry will have the clinical study explained to them, as well as potential risks and benefits of their participation in the study. Each patient who agrees to participate will be required to sign and date an informed consent document prior to the procedure or any study-specific testing. If approved by the local Ethics Committee/IRB, a legally authorized representative may provide consent on behalf of the patient.

If new information is obtained after a patient receives treatment with the device, patients who have not exited the study will be informed about the new

information, and will be reconsented at the discretion of the investigator and/or the site's Ethics Committee/IRB.

8.7 Point of Enrollment

Point of enrollment will be based on the intent-to-treat population, and is defined to include any patient for which the treatment procedure is initiated. More specifically, once a procedure has begun (i.e., cutdown or percutaneous access initiated), this patient would be included in the intent-to-treat population. The patient's informed consent will be obtained and assessment of the patient's conformance to the inclusion/exclusion criteria will occur prior to the procedure.

8.8 Methods

8.8.1. Medication

The hospital's standard protocol should be followed with respect to medication.

8.8.2. Pre-procedure

Grafts are sized based on the findings from preoperative radiologic studies, including computerized tomography (CT) or conventional angiography. Refer to the Instructions for Use for details regarding the suggested imaging studies to be obtained and sizing guidelines.

8.8.3. Procedure

Standard techniques for placement of arterial access sheaths, guiding catheters, angiographic catheters and wire guides should be employed during use of the Zenith Low Profile AAA Endovascular Graft and the Zenith Spiral-Z AAA Iliac Leg Graft. The Zenith Low Profile AAA Endovascular Graft and the Zenith Spiral-Z AAA Iliac Leg Graft are compatible with 0.035 inch diameter wire guides.

Refer to institutional protocols relating to anesthesia, anticoagulation and monitoring of vital signs. Refer to the Instructions for Use for complete details regarding use of the Zenith Low Profile AAA Endovascular Graft and the Zenith Spiral-Z AAA Iliac Leg Graft. Fluoroscopic guidance and angiography should be used throughout the procedure to verify positioning of the devices with respect to the patient's anatomy.

The iliac leg graft should overlap with the main body limb by at least one stent, as inadequate overlap (< 1 stent) may increase the risk for migration and/or endoleak. Excessive overlap of the iliac leg graft with the main body (leg component more than 10 mm above the main body bifurcation) may restrict flow and thereby increase the risk of limb thrombosis. Additionally, the proximal edge of the ipsilateral leg graft should align closely with that of the contralateral leg graft (i.e., the ends of both graft legs should be at the same height relative to the graft bifurcation).

If the distal seal of the iliac leg graft lands in a location different from that used to select the graft size, undersizing or excessive oversizing could result. Excessive oversizing may result in flow restriction with higher risk of limb thrombosis and should be treated appropriately at the time of procedure (e.g., with adjunctive balloon dilatation and/or stent placement).

Pre-existing regions of stenosis/narrowing less than approximately 20 mm ID in the aorta or 7-8 mm ID in the iliac arteries may increase the risk for limb thrombosis if left untreated. Dilatation of these regions with a noncompliant balloon and/or stent placement may be necessary to help assure continued graft patency. The completion angiogram (with stiff wire guides removed) should be reviewed carefully to determine whether further treatment in these regions is necessary (e.g., adjunctive balloon dilatation/stent placement). Failure to remove the stiff wire guide prior to the angiogram could mask any limb kinking or narrowing that might occur when the wire guide is removed.

Both graft leg lumens should be evaluated carefully in multiple views at the completion of the procedure to assess for any narrowing and to document the minimum graft lumen ID. Patients with a graft leg lumen less than approximately 5 mm ID may be at increased risk for limb thrombosis. Intervention (e.g., noncompliant balloon dilatation and/or stent placement) should be considered to help assure continued graft patency.

8.8.4. Peri-operative Care

The endovascular method does not require any departure from the usual peri-operative management of patients undergoing aneurysm repair.

8.8.5. Post-operative Treatment of Endoleaks

Type I and type III endoleaks warrant immediate treatment. Type II endoleaks should be treated at the physician's discretion, depending on aneurysm behavior and size, endoleak source, and time from implantation. If the aneurysm is enlarging, treatment by embolization or ligation should be considered. Type III endoleaks should be treated with additional ballooning or prostheses.

8.9 Criteria and Procedures for Study Termination

A patient's follow-up in the study will end after:

- 1) Failure to deploy the device + 30 days;
- 2) Conversion to open surgical technique + 30 days;
- 3) Patient withdrawal or lost to follow-up;
- 4) Patient death;
- 5) Closure of the investigation; or
- 6) Completion of all scheduled clinical and imaging visits through 5 years.

No medical care related to the clinical study will be provided for the subjects after study completion.

8.10 Sample Size

This investigation will enroll a maximum of 120 subjects at a maximum of 40 investigative sites. Patient recruitment is expected to be completed within 12 months of initiating the study. Follow-up data will continue to be collected for 5 years after graft deployment for each patient in the study, making the study duration at least 72 months.

8.11 Period of Use for the Device or its Control

The 5-year follow-up period of the clinical investigation should permit the demonstration of performance over a period of time sufficient to represent a realistic test of the performance of the device and allow identification and risk assessment of any associated adverse device effects over that period.

8.12 Limitations of the Investigation

This study is inherently limited by the number of patients who will be excluded due to general, medical, and anatomical exclusion criteria. Additional challenges of the study include the anticipated comorbidities likely to be found in patients with aortic, aortoiliac, or iliac aneurysms, which may confound data analysis.

Additional confounding elements of the study might include the lower incidence of AAA in women, with the anticipation of fewer women than men being enrolled in the study.

8.13 Safety Monitoring

Safety monitoring will include collecting data regarding adverse events. Section 7, Risk Analysis, lists the potential adverse events associated with this study.

A Data Safety Monitoring Board (DSMB) consisting of independent physicians and at least one independent statistician, who are not investigators in the study, nor have a perceived conflict of interest with the conduct and administration of the study, will be convened on a regular basis to evaluate the study progress and review adverse events.

An independent Clinical Events Committee (CEC) will be established to adjudicate clinical events reported during the study. This adjudication will be performed according to standard operating procedures to assess whether the events were due to a pre-existing condition, procedure-related, technique-related, and/or device-related. In addition, a core lab will be established to independently review available imaging.

Regular scheduled monitoring, including on-site visits, will be conducted, in part, for identification of adverse events and assurance that they are correctly reported to the DSMB, CEC, and Ethics Committees/IRBs.

In addition, incidences of intra-operative conversion to open surgical aneurysm repair, access failure, and intra-operative type I or type III endoleak will be evaluated by the sponsor on a case-by-case basis. If a potential safety issue is identified, the sponsor may delay additional enrollment until further investigation into the incident is performed.

9.0 Statistical Considerations

9.1 Sample Size Calculations

Evaluation of the safety hypothesis, 30-day freedom from MAEs, requires 46 patients to determine whether the performance goal of 88% has been met.

Evaluation of the effectiveness hypothesis, 12-month device success, requires 59 patients to determine whether the performance goal of 83% has been met. Cook intends to enroll 120 patients to account for patients who withdraw or are lost to follow-up, and also to provide added enhanced statistical certainty as well as the same number of patients as agreed to for a previous similar study.

Sample size calculations for the safety and effectiveness hypotheses can be performed with the following assumptions. Using performance goals of 88% for freedom from MAEs and 83% for device success, with an expected rate of 99.2% for freedom from MAEs and 93.5% for device success, an exact binomial calculation, $\alpha=0.025$, power=0.80 and a one-sided test, 46 patients for freedom from MAEs and 59 patients for device success are required to demonstrate that the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft meets the stated performance goals.

9.2 Performance Goals

The performance goals used for the hypotheses in section 4.3 and the sample size calculations in section 9.1 were derived from the pivotal study of the Zenith AAA Endovascular Graft. The 30-day freedom from MAEs was 98.3% and the 12-month device success was 93.0% in the pivotal study of the Zenith AAA Endovascular Graft. Therefore, the performance goals of 88% for freedom from MAEs and 83% for device success, respectively, have been determined.

9.3 Site-level Poolability

Poolability of data from multiple sites will be verified by examining the safety and efficacy measures as well as important patient baseline characteristics among sites. Site-level poolability will be considered appropriate provided that these measures are similar among sites.

[REDACTED]

[REDACTED]

[REDACTED]

9.4 Missing Data

Missing data will be addressed using three primary strategies: 1) estimating missing data with the best available data, 2) case deletion, and 3) multiple imputation.

The first strategy may be used for missing imaging data. Previous clinical trial experience suggests that some portion of the imaging data may not meet the criteria for accurate measurements by the core laboratory. However, it is recognized that the treating physician uses this information to provide the best possible care for the patient. Therefore, it is reasonable to substitute any missing core laboratory measurements with the corresponding measurements made by the treating physician (or his/her staff). In addition, the absence or presence of clinical sequelae may provide the required missing core laboratory assessment of device performance. This strategy is a best approximation of the missing data value.

The second strategy is case deletion. If the amount of missing data does not result in a reduction of analyzable patients to a number that is below that required for sufficient statistical power of the endpoints, then case deletion will be the method of choice for that analysis.

The third method is multiple imputation. This method will be used to predict missing endpoint or covariate data. It may be that the study endpoints may

depend upon certain covariates. Therefore, it may be possible to model study endpoints, given a series of related covariates. This model-based imputation exercise may provide estimates of the missing data that can be utilized in estimating event rates and confidence bounds.

9.5 Future Use of Study Data

The data collected in this study may be used to justify additional studies of variations on the Zenith Low Profile AAA Endovascular Graft including, but not limited to, design variations. It is anticipated that the safety and effectiveness data obtained may serve as prior information in the analysis of the safety and effectiveness of future variations of the Zenith Low Profile AAA Endovascular Graft.

10.0 Emergency Situations

Patients will not be treated with the Zenith Low Profile AAA Endovascular Graft in conjunction with the Zenith Spiral-Z AAA Iliac Leg Graft in emergency situations where prior consent of the patient is not possible.

11.0 Deviations from Clinical Investigation Plan

Investigators are not allowed to deviate from this Clinical Investigation Plan without prior authorization by the sponsor except under emergency situations when necessary to preserve the rights, safety, or well-being of study patients.

Deviations or noncompliances will be recorded together with an explanation. Deviations or noncompliances that impact the rights, welfare, or safety of patients shall be reported to the sponsor and Ethics Committee/IRB as required and as soon as possible. If appropriate, corrective and preventive actions will be discussed by the sponsor, investigator, and/or the Ethics Committee/IRB to determine a suitable course of action.

When available, the reasons for withdrawal and discontinuation of any patient from the investigation shall be recorded. If such discontinuation is because of problems with safety or lack of effectiveness of the device, that patient shall still be followed-up in the investigation, if possible.

12.0 Procedure for Reporting Adverse Events and Adverse Device Effects

Events known to be related to pre-existing conditions or existing at admission are not considered adverse events (e.g., prior medically-treated cardiac arrhythmia with no change in status during the endovascular procedure). Additionally, common standard of care practices are not considered adverse events (e.g., centers located at high geographical altitudes that discharge all patients on home oxygen therapy regardless of procedure).

All adverse events (i.e., device-related and non-device-related) are to be reported using the appropriate case report form (Adverse Event/Complication form). In cases of adverse device effects (adverse event with relation to the study device) or serious adverse events, completed forms should be submitted to the Data Coordinating Center as soon as possible upon knowledge of the event.

MED Institute, Inc.
1 Geddes Way
West Lafayette, IN 47906
Telephone: [REDACTED]
Fax: [REDACTED]

The Data Coordinating Center will notify the sponsor/manufacture accordingly. In accordance with applicable requirements, the investigator will notify the local Ethics Committee/IRB, while the sponsor/manufacture will notify the regulatory authority. Furthermore, if the sponsor determines that the device presents a potential risk to the study patients, all investigators in the study will be notified. Clinical sites will be responsible for following their normal reporting process (e.g., to manufacturer, to regulatory authority) for any problems with the commercially available devices. Refer to section 7.1 for a list of potential adverse events related to this study.

13.0 Ethical Considerations

13.1 Declaration of Helsinki

The investigation shall be performed according to the ethical principles that have their origin in the Declaration of Helsinki and in accordance with ISO 14155, ICH GCP, and 21 CFR 812.

13.2 Ethical Approval

The investigator is responsible for obtaining approval of this clinical investigation by the relevant Ethics Committee/IRB, and the clinical study will not begin until a favorable opinion of the Ethics Committee/IRB has been obtained. The sponsor must be provided with a copy of this approval before delivery of any study device. The investigator is responsible for complying with the requirements imposed by his/her Ethics Committee/IRB and/or regulatory authority. Furthermore, the investigator will ensure that local regulations concerning data protection are followed.

14.0 Early Termination or Suspension of the Investigation

The sponsor reserves the right to terminate/suspend the study at any point should they believe that important harmful events might result from its continuation. If a decision is made to terminate the study, all patients already treated will be followed according to the study follow-up schedule. Subjects may withdraw from the study at any time without penalty or loss of benefits. The subject should notify the investigator of his/her desire to withdraw. The investigator may also decide to withdraw a subject from the study at any time on the basis of medical judgement. In any case, the reasons for withdrawal will be documented, when available.

15.0 Publication Policy

Publication and presentation policies are outlined in the study contractual documents.

16.0 Data Collection

Patient data will be collected and entered by trained personnel at the clinical site onto electronic Case Report Forms (eCRFs) through an electronic data capturing (EDC) system. This is a secure, web-based system, allowing those with permission to access data from any location at any time. Source data are to be retained for data entered into the EDC system. Data obtained and simultaneously entered into the EDC system may also serve as source documentation.

Site personnel are required to undergo data entry training and will have unique login names and passwords in order to enter patient data. In accordance with 21 CFR Part 11, the EDC system creates a secure, computer-generated, time

stamped audit trail to record the date and time of operator entries and actions that create, modify, or delete electronic records.

17.0 Data Reporting

Progress reports and a final report at the conclusion of the clinical investigation will be submitted by the investigators and sponsor to the regulatory bodies and Ethics Committees/IRBs as required by local regulations.

Attachment 1
Written Procedures for Monitoring Studies

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Attachment 2
Definitions

Proximal Neck: Infrarenal aortic segment from the lowest level of the distal-most renal artery intended to remain patent, to the proximal end of the aneurysmal aorta.

Calcification: Calcification will be graded based upon the following:
None: Absence of calcification;
Mild: Less than 40% circumferential calcification;
Moderate: 40-70% circumferential calcification; or
Severe: Greater than 70% circumferential calcification.

Tortuosity of Iliac Arteries: Tortuosity will be graded based upon the following:
None: No tortuosity;
Mild: Minimal tortuosity (less than one turn involving either external or common iliac artery);
Moderate: Single turn involving either external or common iliac artery; or
Severe: Compound turns involving external and common iliac arteries.

Occlusive Disease of Iliacs: Occlusive disease will be graded based upon the following:

None: Absence of occlusive disease;
Mild: Some disease, focal with less than 30% narrowing;
Moderate: Between 30-50% narrowing not requiring; interventional techniques to meet entry criteria; or
Severe: Greater than 50% narrowing or any patient requiring angioplasty prior to endograft delivery.

New York Heart Association Classification:

- 1 Patient with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity

- does not cause undue fatigue, palpitation, or dyspnea.
- 2 Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest, ordinary physical activity results in fatigue, palpitation, or dyspnea.
 - 3 Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest, less than ordinary physical activity causes fatigue, palpitation, or dyspnea.
 - 4 Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Disabling Chronic Obstructive Pulmonary

Disease (COPD): Having a forced expiratory volume (FEV₁) <1.0 liter or receiving home oxygen therapy.

Intractable

Hypertension: Having a systolic arterial pressure >160 mmHg despite receiving medication.

MI (Non-Q-Wave): Investigator identified patients having clinical evidence of a myocardial infarction with elevated peak CK values greater than or equal to three times the upper limit of normal with elevated CK-MB (above the institution's upper limit of normal) in the absence of new pathological Q-waves or clinical evidence of a myocardial infarction with troponin greater than three times the upper limit of normal, as determined by the investigator.

MI (Q-Wave): Post-procedure presence of new Q-waves greater than 0.04 seconds in at least two EKG leads.

- Renal Failure:* Acute or progressive renal insufficiency leading to the need for dialysis or hemofiltration.
- Renal Insufficiency:* A rise in serum creatinine of more than 30% above the pre-procedure level, resulting in a serum creatinine level >2.0 mg/dl that does not spontaneously resolve (does not include those patients with a pre-procedure serum creatinine >2.0 mg/dl).
- Embolization:* Clinical evidence of ischemic tissue remote from the operative field, presumably caused by thrombus dislodged from the aneurysmal sac, aortic neck, or adjacent vessels, including ischemia of the kidneys, pelvis (IIA) or lower limbs. This is, of course, distinct from intentional pre-operative, operative, or post-operative embolization procedures.
- Graft Limb Occlusion:* The presence of thrombus within one, or both, of the graft limbs (including any legs and extensions) creating complete occlusion with no blood flow through the graft limb.
- Graft Lumen Diameter:* The diameter measured inner wall to inner wall within the endograft.
- Type I Endoleak:* A peri-prosthetic leak occurring at the proximal and/or distal fixation zones.
- Type II Endoleak:* A leak caused by retrograde flow from patent lumbar or inferior mesenteric arteries or other collateral vessels.
- Type III Endoleak:* A leak caused by a defect in the graft fabric, or inadequate seal of modular graft components.
- Type IV Endoleak:* A leak caused by graft fabric porosity, often resulting in a generalized blush of contrast within the aneurysm sac.

Endoleak (early): Any endoleak observed within 30 days of device deployment.

Endoleak (late): Any endoleak observed later than 30 days after device deployment that was not documented during the first 30 days post-deployment.

Radiographic Migration

(stent-graft): Antegrade or retrograde movement of the stent-graft ≥ 10 mm at the level of the renal arteries as compared to the position on the first post-operative CT scan.

Clinical Utility

Measures: Duration of procedural intubation; days to resumption of oral fluids; days to resumption of normal diet; days to resumption of normal bowel function; days to ambulation; duration of ICU stay; days to discharge.

Clinically Significant Migration

(stent-graft): Antegrade or retrograde movement of the stent-graft requiring surgical or endovascular intervention.

Barb Separation: Radiographic evidence of detachment of barbs from the stent strut as confirmed by the CEC.

Stent/attachment System

Fracture/break: Fracture or breakage of any portion of the stent or attachment system including metallic fracture or breakage of any suture material used to construct the stent or secure the stent or attachment system to the graft material as confirmed by the CEC.

Technical Success: Successful access of the aneurysm site and deployment of the Zenith Low Profile AAA Endovascular Graft and the Zenith Spiral-Z AAA Iliac Leg Graft in the intended location. The endovascular graft must be patent at the

time of deployment completion as evidenced by intraoperative angiography.

Device Success

(12-month):

Technical Success, with none of the following at 12 months:

- Type I or type III endoleaks requiring re-intervention;
- Graft limb occlusion;
- Aneurysm rupture or conversion to open surgical repair; or
- Aneurysm enlargement greater than 0.5 cm.

Major Adverse Events: All-cause death, Q-wave MI, renal failure requiring dialysis, paralysis, stroke, bowel ischemia, re-intubation.

Serious Adverse

Event:

An adverse event that led to death, led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury, resulted in a permanent impairment of a body structure or a body function, required in-patient hospitalization or prolongation of existing hospitalization, resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, led to fetal distress, fetal death, a congenital abnormality or birth defect.